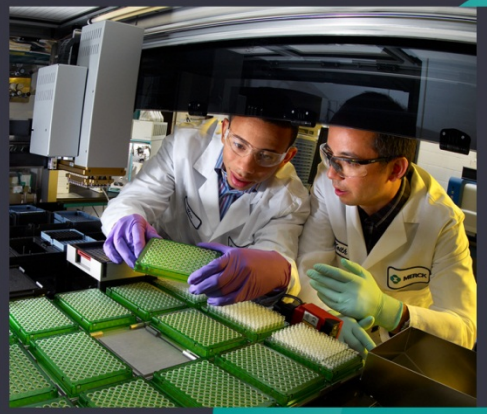
Fall 10-19-2015

# Single use sensors: Sensing a need for change

David Pollard
*Merck & Co*

# Single Use Sensors:
## *Sensing a Need for Change*


**David Pollard**

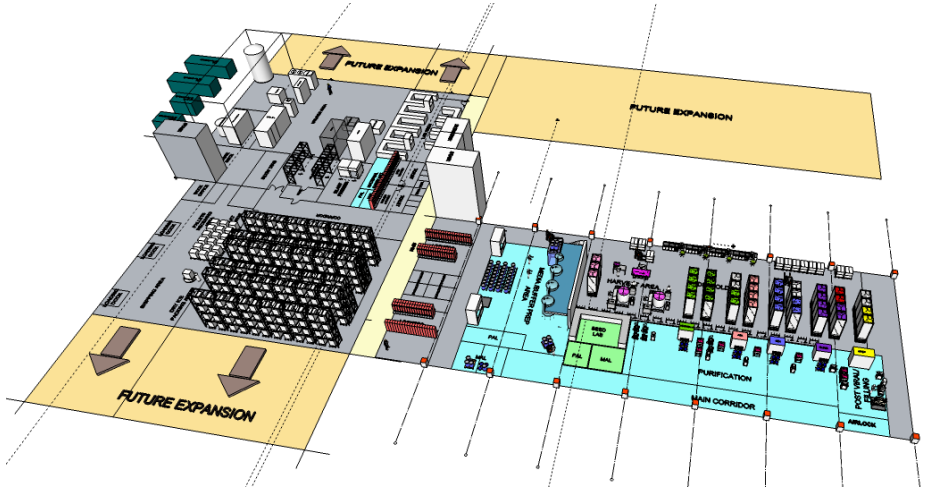
**BioProcess Development**
**Merck Research Labs**
**Merck & Co. Inc**
**Whilworth, NJ**

# Transitioning to Next Generation Manufacturing

## Stainless Steel

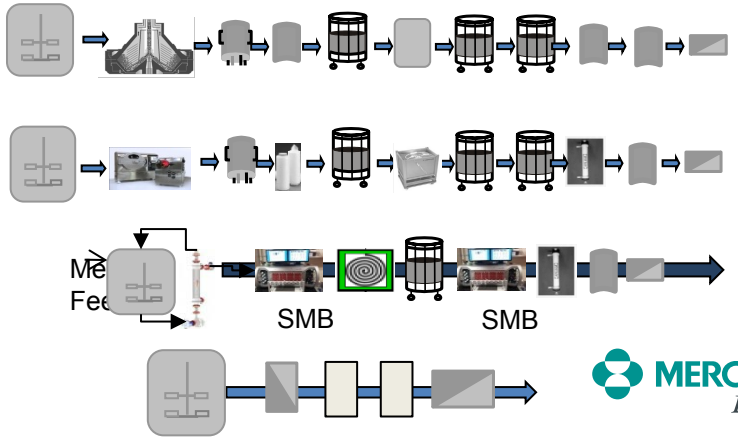
- Internal Stainless Expertise
- Significant capital investment
- Fed Batch Processing
  - Limited PAT & Process control

## Single Use




- Low cost, agile manufacturing
- SU, PAT & Automation enabled

FoF with flexible responsive toolbox of process platforms



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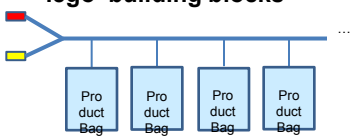
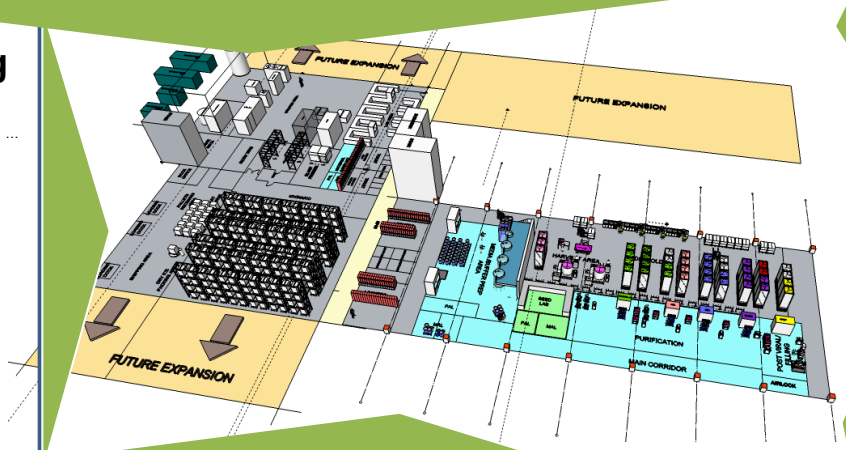
# Facility of the Future
## *CHO mAb Processing Vision*

### Automated Continuous Processing

### Component Engng
'lego' building blocks

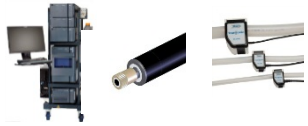



**Molded parts**

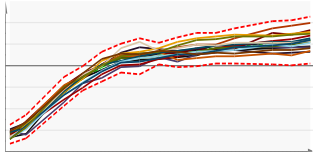



### Adaptive Process Control

PAT tools



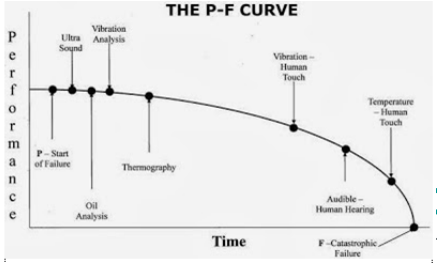
Predictive MDVA models



Real Time Release Testing

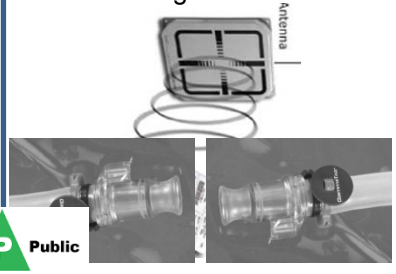
### Equipment Performance Real time Monitoring

Examples:
Real time sensing of Pump seal failure, PAT sensor performance
•Proactive preventative maintenance to limit failures
•Eqpt redundancy strategy
•Process flow strategy for deviations




### SU operations

Automated Inventory management




Single use Workflows
Buffer supply
Fluid flow management



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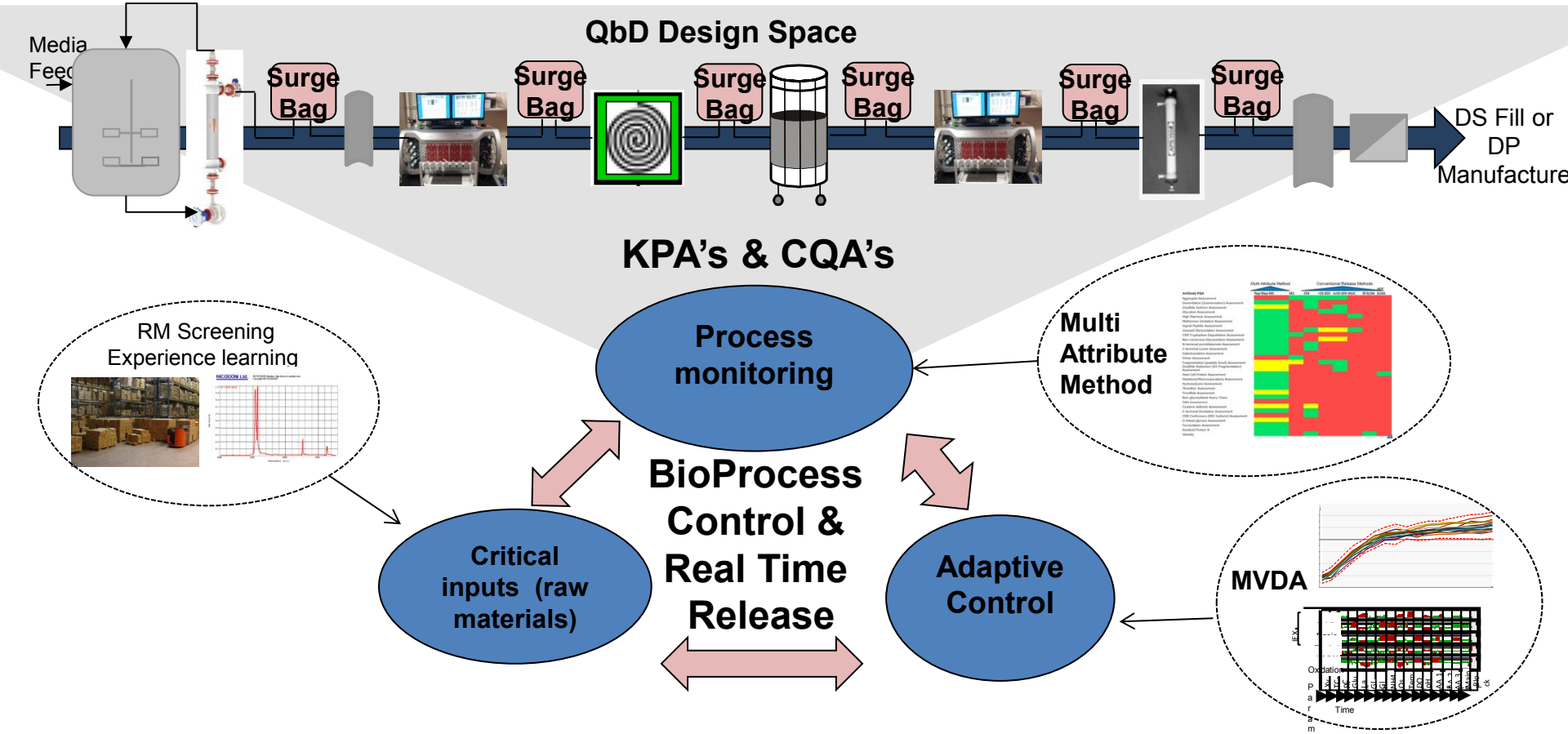
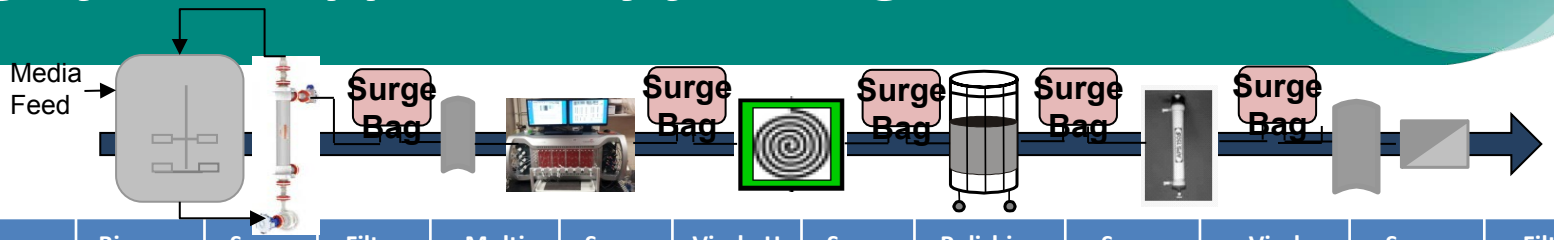
# Attribute & Process Control Opportunity




- End Product QC Testing transition to Real Time Release Testing
- Real time automated control: process responds to variability & disturbances
  - End to end prediction models for complete process
  - RM control ➡ Process input ➡ Product quality & yield

# Process Monitoring & Control :
## *Significant Opportunity for Single Use Sensors*



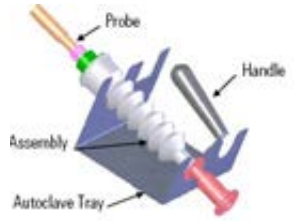

| | Bioreactor | Surge Bag | Filter | Multi Column Chrom | Surge bag | Viral pH inactivation | Surge Bag | Polishing Chrom | Surge Bag | Viral Clearance | Surge Bag | Filter | UF/DF conc |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Pressure** | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| **pH** | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| **Flow** | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| **DO** | ✓ | | | | | | | | | | | | |
| **Biomass** | ✓ | | | | | | | | | | | | |
| **Level** | ✓ | ✓ | | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ |
| **Conductivity** | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ |
| **Metabolite** | ✓ | | | | | | | | | | | | |
| **Product Conc** | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ |
| **Product quality** | ✓ | ✓ | | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ |
| **Aseptic** | ✓ | ✓ | | | ✓ | | ✓ | | ✓ | | ✓ | | |

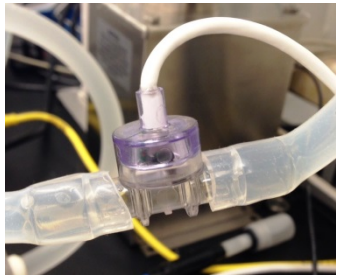
# Barriers to SU Sensor Implementation:

| Barrier | Summary |
|---|---|
| Significant Technology Gaps | Lack of Technology Options |
| | Reliability & Robustness Concerns |
| | Accuracy & Drift |
| | Limited offerings only in one image (inline only with one tubing size, not bag adaptable) |
| | High Cost |
| Lack of Clearly Defined End User Expectations | Misalignment between End users & Suppliers on SU GMP expectations |
| Lack of Industry alignment on quality / validation strategy for SU sensors | Need aligned Calibration & Implementation guidance for SU Sensors |

# Examples of Technology Gaps

| Parameter | Current state issues |
|---|---|
| pH | SU only pH 7 : needs to be 4-7<br>Insertion of Glass electrode with calibration requirement |
| DO | Optical : patch stability, media interference |
| Conductivity | Gamma stable only, not steam sterilizable<br>Robustness concerns |
| Pressure | Gamma stable , not steam sterilizable<br>Robustness concerns |
| Capacitance | Selectivity concerns, limited SU offerings |
| Flow | Accuracy issues and insufficient ranges<br>Robustness & reliability |
| Metabolites & Osmolarity | Limited SU offerings |
| Bio burden testing | No inline direct methods |
| Aseptic sampling | Available cell free sampling<br>Issues of sampling cell containing solutions |





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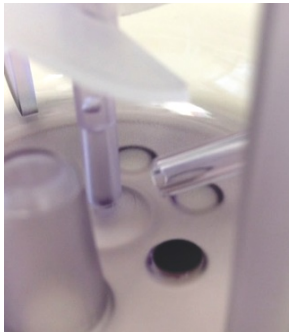
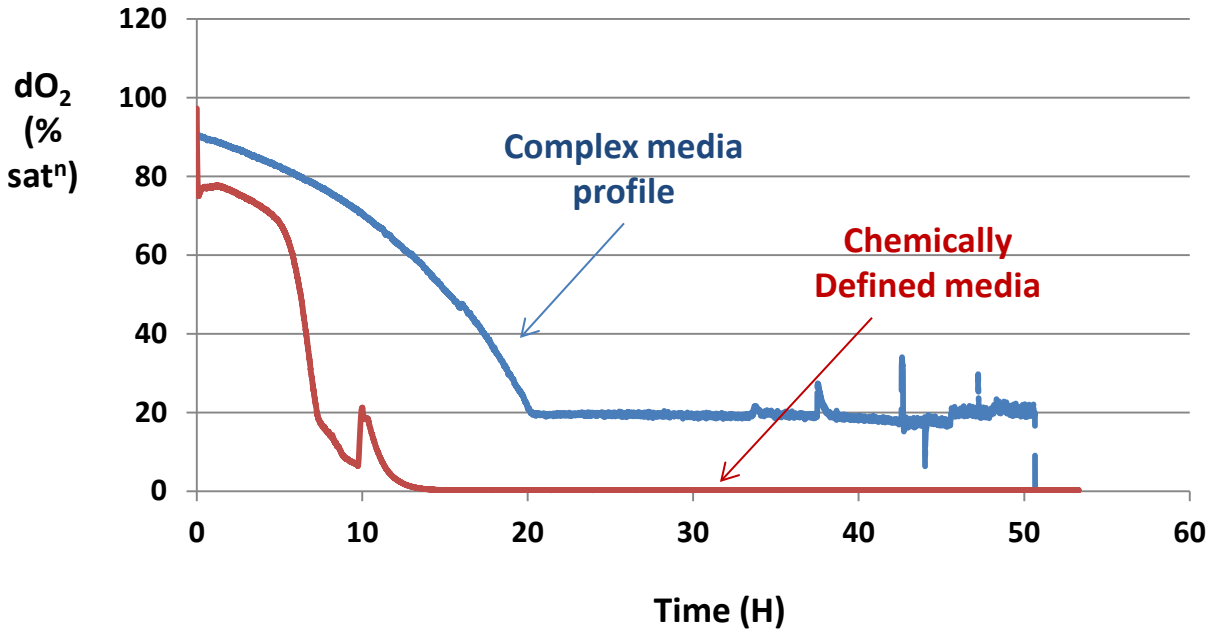
# Technology Gap Example:
# *Media Interference to Fluorescence $dO_2$*

## Fluorescence patch $dO_2$ sensor

- Well established performance in complex media
- Poor performance in chemically defined media



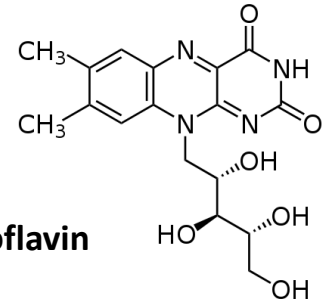



**Hypothesis**:

**Interference from media components with strong fluorophore**

**Vitamin, riboflavin interference**

**Effect masked in complex media Hydrolysates**




**Riboflavin**

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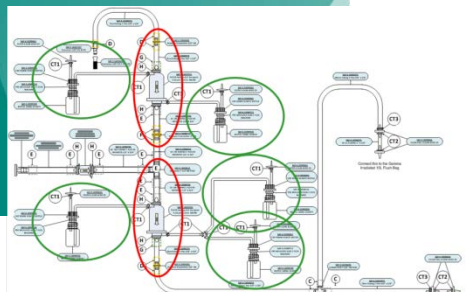
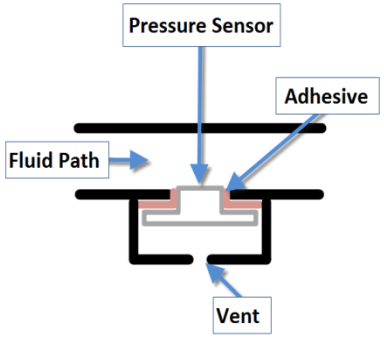
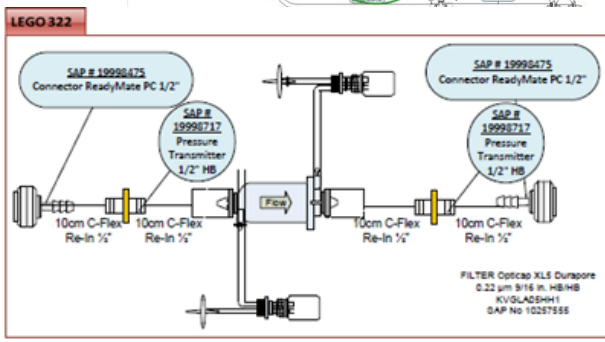
# Technology Gap Example:
# *Autoclave Tolerant Pressure Sensor*



**Problem Statement:**

- Sensor integrity failure post autoclave sterilisation leading to sterile boundary leak.



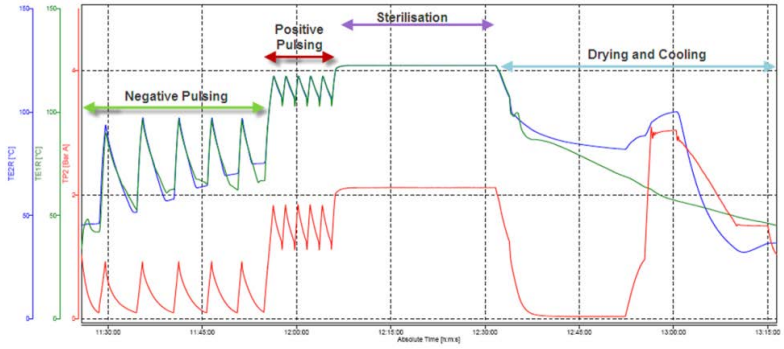




**Application:**

- Integrated into final filtration manifold
- Measure control filter Delta P
- Trigger for safety interlock.

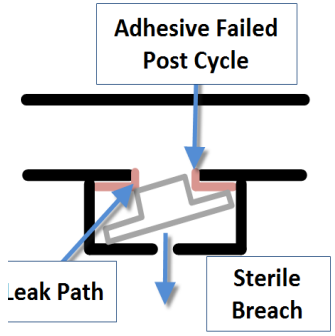
**Investigation:**

- Investigation was able to recreate defect in autoclave.
- Demonstrated weakened sensor membrane adhesive post autoclave cycle.
- Performed in-conjunction with vendor




**Root Cause:**

- High temperature combined with extended vacuum pulses creates Delta P across sensor membrane / vent.
- Resulting in adhesive fatigue leading to leak path and sterile breach.




*Chris Roberts*
*MSD Carlow*

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# SU Sensor Expectations

| Expectations | |
|---|---|
| Stable for 30 - 100 day duration (perfusion & continuous processing) | Capable of reuse (eg. buffer bag refill ) |
| Selectivity | Linearity of response |
| Sensitivity | Reproducibility of signal response |
| Fast response & recovery time | Measurement Temperature tolerant up to 80 DegC (hot WIFI applications) |
| Gamma (25-40 kGY) and Steam Sterilizable | Multiple image options: inline tubing sizes 1/8, ¼, 3/8, ½, ¾, 1, 1.5 2, Bag welded patch |
| SU material compatibility and bonding standards Class VI compliant | Ability for Feedback control |
| Wireless Capable | Comply with SU guidance expectations |

***Single Use Sensing to be as robust & reliable as Stainless Steel Technology***

# Merck Supplier Expectations for Properly Qualified/Validated SUT

***Consistent information required to guide SU equipment selection***

- **Section 1 – Biocompatibility**
- **Section 2 – Mechanical Properties**
- **Section 3 – Gas/Vapor Transmission**
- **Section 4 – Compendial Physicochemical Properties**
- **Section 6 – TSE-BSE**
- **Section 7 – TOC Analysis**
- **Section 8 – pH/Conductivity**
- **Section 9 – Extractables and Leachables**
- **Section 10 – Chemical Compatibility**
- **Section 11 – Protein Adsorption Studies**
- **Section 12 – Endotoxin Testing**
- **Section 13 – Sterilization Validation**
- **Section 14 – Container Closure Integrity (CCI)**
- **Section 15 – Particulates USP <788>, EP 2.9.19**
- **Section 16 – Calibration of Embedded Instrumentation**

# Merck Supplier Expectations for Properly Qualified/Validated SUT

**ATTRIBUTE 16– CALIBRATION of EMBEDDED INSTRUMENTATION**

**16.1 Provide traceable calibration certificates (per instrument) that comply with international standards such as NIST/UKAS.**

**16.2 Provide the calibration expiration date**

**16.3 Provide verification that the instruments can be independently calibrated pre and post use and provide guidance on how this can be executed.**

**16.4 Provide specific calibration range and loop tolerance details of the integrated instrument/ ie element/indicator/other.**

**16.5 Provide data regarding the shelf life of the instrumentation and whether the instruments can be recycled by Merck.**

**16.6 Provide data regarding how stable the embedded instrumentation is to cleaning and sterilization processes. Vendor expected to provide data.**

**Supplier to provide technical verification regarding connectivity of instruments to Merck control systems (Delta V etc)**

# GMP Implementation/Calibration Guidance

- **Implementation assisted by ongoing SU Initiatives**

| | |
|---|---|
| SUT Design & Verification (BPSA & ASTM) | SU User Requirements (BPOG/BPSA) |
| SUT Supply Chain (BPSA) | SUT System integrity |
| SUT Change Notification (BPOG/BPSA) | |

  - Consider Sensor Standardization at appropriate time of technology maturity
    - Align with SU assembly catalogs (PM Group)

- **Alignment on Calibration Guidance**
  - ***Issue*: Post Process Calibration can be difficult for SUT**
  - ***Proposal*: Application Specific Procedures Required (Case by Case Basis)**
    - **<u>GMP critical measurement</u>**: confirm calibration with post process measurement from secondary test
      - Examples pH for upstream when known to impact product quality, conductivity of feed stream for polishing chrom, online UV for polishing chrom cuts for aggregate decision
    - **<u>GMP Non Critical</u>**; No post process calibration required
      - Examples : $dO_2$ for upstream processing, inline pressure monitoring for filtration, inline UV concentration for UF step
    - Collect examples and publish industry guidance (BPOG/BPSA)

# SU Sensor User Criteria: *Upstream*

| Function | Range | Accuracy | Drift | Resolution | Calibration | Duration of operation | Additional Comments |
|---|---|---|---|---|---|---|---|
| pH (Upstream) CHO cell culture | pH 6.5-7.5 | +/- 0.05 | < 0.01 pH per day | +/- 0.01pH | Factory pre calibrated One point check acceptable by either check standard fluid or process media | Fed batch processes 14-20days Perfusion upto 60days | Current state technology : Drift >0.05 unit /day, & reliability not acceptable, ionic strength sensitive. Lifetime issues for < 14days expts |
| pH (Upstream) Microbial | pH 5.5 to 8 | +/- 0.1 | < 0.01 pH per day | +/-0.01 pH | Factory pre calibrated One point check acceptable by either check standard fluid or process media | < 7 days | Drift, reliability not acceptable, ionic strength sensitive |
| Dissolved oxygen (upstream) | 0-100% air saturation 0-1400 umol/L | +/- 0.05% O2 at 0.2% O2 | < 0.03% O2 within 30days | +/- 0.01%O2 at 0.21% O2, +/- 0.1%O2 at 20.9% O2 | Factory set but in process calibration acceptable | Fed batch processes 14-20days Perfusion upto 60days | Fast Reponses time required < 6 secs, ideally < 2 secs |
| Temperature (upstream and downstream) | 0-4-deg C to 70 deg C | +/- 0.1 C | < 0.01 deg C | 0.01 deg C | Factory set. Annual field cal (unlikely to be throw away element) | Upto 60 days | Cell culture in 32 to 37 degC Need cooling capability to 4 degC Downstream in 18 to 22 deg C |
| Pressure | 0 to 10 Psi | +/- 0.1 Psi | < 0.1 / month | 0.01 Psi | Factory set Possible Post use cal | Upto 60 days | Pressure safety monitoring to avoid over expansion/rupture of bioreactor vessel bag |

# SU Sensor User Criteria:
# *Upstream Metabolites*

| Pichia | Concentration Range |
|---|---|
| Methanol | 0-40 g/L |
| Ammonia | 0-10 g/L |
| Glycerol | 0-40 g/L |
| Sorbitol | 0-20 g/L |
| Biomass | 0-500 g/L WCW |
| Product (mAb or TP) | 0-2.5 g/L |
| Antifoam (UCON) | 0.7-10 mL/L |
| Phosphate | 0-20 g/L |
| pH | 4.5 to 6.5 |

| E.coli | Concentration Range |
|---|---|
| Ammonia | 0-10 g/L |
| Glycerol | 0-20 g/L |
| Glucose | 0-20 g/L |
| Acetate | 0-10 g/L |
| Biomass | 0-250 g/L WCW |
| Product | 0-10 g/L |
| Antifoam (Sigma 204) | 0.195-0.3 mL/L |
| Citric acid | 0-2 g/L |
| Phosphate | 0-5 g/L |
| pH 4 to 7 | |

| CHO | Concentration Range |
|---|---|
| Lactate | 0-40 mM |
| Ammonia | 0-15 mM |
| Glucose | 0-60 mM |
| Biomass | 0-20 e6 cells/mL |
| Product (mAb or TP) | 0-5 g/L |
| Viability | 0-100 % |
| Osmolality | 150-450 mOsm/kg |
| Glutamine | 0-8 mM |
| Glutamate | 0-8 mM |
| Dow Antifoam C | 0-1 mL/L |
| pH 7 | |

# SU Sensor User Criteria: *Purification*

| Function | Range | Accuracy | Drift | Resolution | Calibration | Duration of operation | Additional Comments |
|---|---|---|---|---|---|---|---|
| pH (Downstream) | pH 3 to 10 | +/- 0.05 | < 0.01 pH per day | +/- 0.01 pH | Factory pre calibrated<br>One point check acceptable by either check standard fluid or process media | Up to 60 days | Two point cal would be a requirement here over such a wide range |
| Temperature (downstream) | 4 deg C to 25 DegC | +/- 0.1 C | < 0.01 deg C | 0.01 deg C | Factory set Annual field cal (unlikely to be throw away element) | Up to 60 days | Downstream in 18 to 22 deg C<br>Need cooling capability to 4 degC<br>compatible with 0.1M NaOH |
| Conductivity (Downstream) | 1 uS/cm to 200 mS/cm | +/- 0.25 mS in 10-200mS range | Stable (60day sh) | | Factory set | Up to 60 days | Temp range 4-50 degC, compatible with 0.1M NaOH |
| Pressure | 0 to 40 Psi | +/- 1 Psi | < 0.1 / month | 0.1 Psi | Factory set Possible Post use Cal | Up to 60 days | Pressure for filtration and/ or tangential flow filtration. Assumes a feed inline pressure of up to 40 Psi, Assumes inline application |
| Flow<br>Two flow rate ranges required | 10mL/min to 150mL/min<br><br>1.5L/min to 20L/min | +/- 3% | < 1% month | | Factory set, fluid type independent | Up to 60 days | Inline flow analysis<br>Tubing sizes<br>Tubing #16 (ID 3mm, 1/8”) up to 1” inner diameter |
| Inline UV | 200-1025nm (0-4AU | 0.02 AU | < 0.1 AU/month | 0.03 to 10nm | Auto Zero<br>Factory set | Up to 60 days | Flow thru measurement |

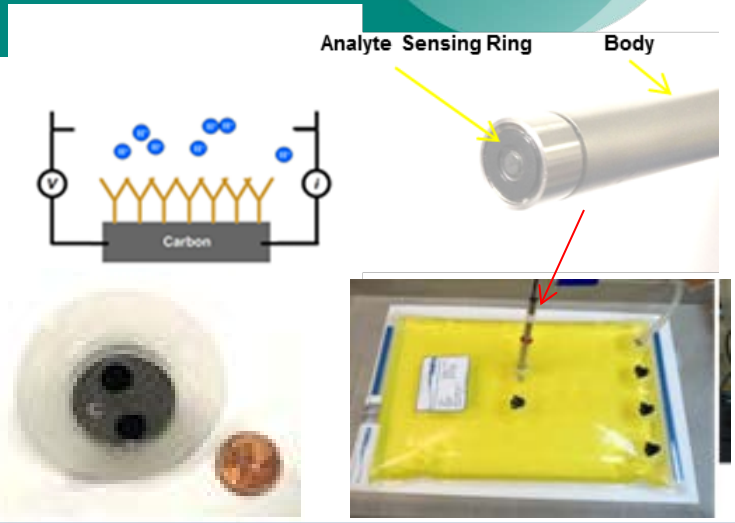
# Potential Next Gen SU Sensors: *solid state pH*

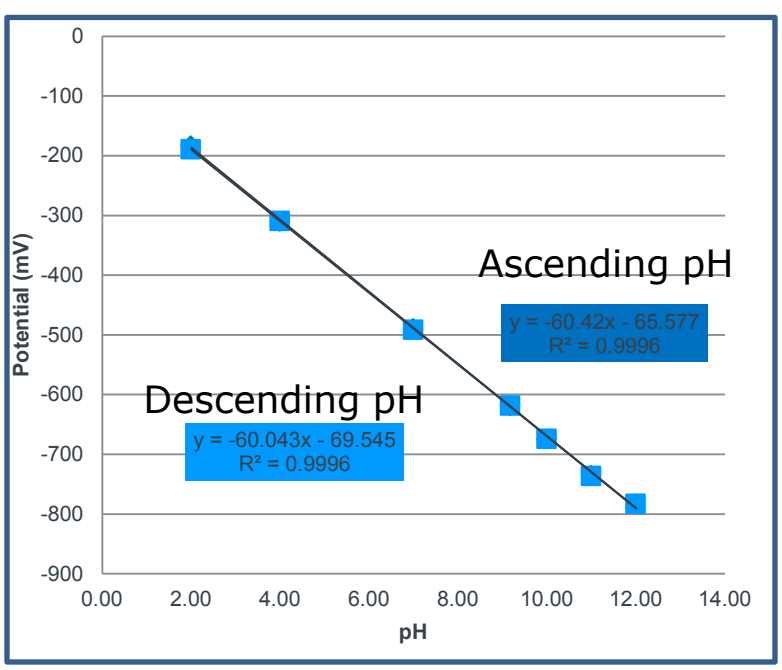
SENOVA SYSTEMS
BEYOND MEASURE

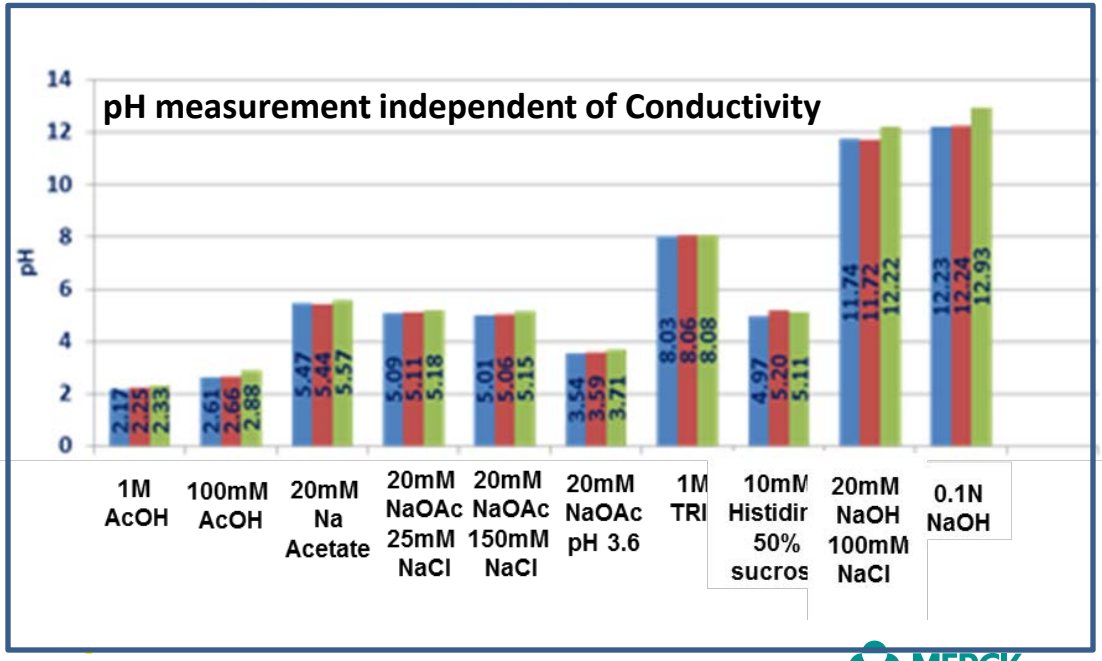
**Direct pH measurement at conductive surface by Analyte Sensing Molecules**

**pH response is intrinsic; requires no user calibration**

**Eliminate glass electrodes & demonstrated for use in Single Use Systems applications**

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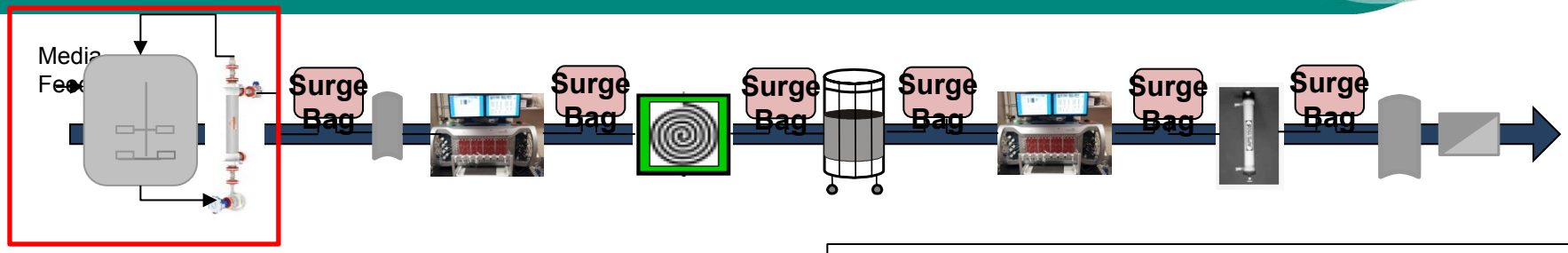
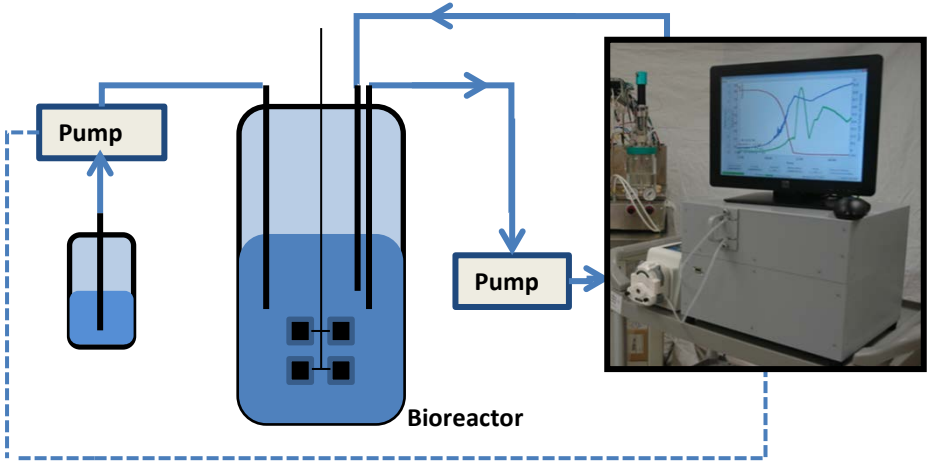
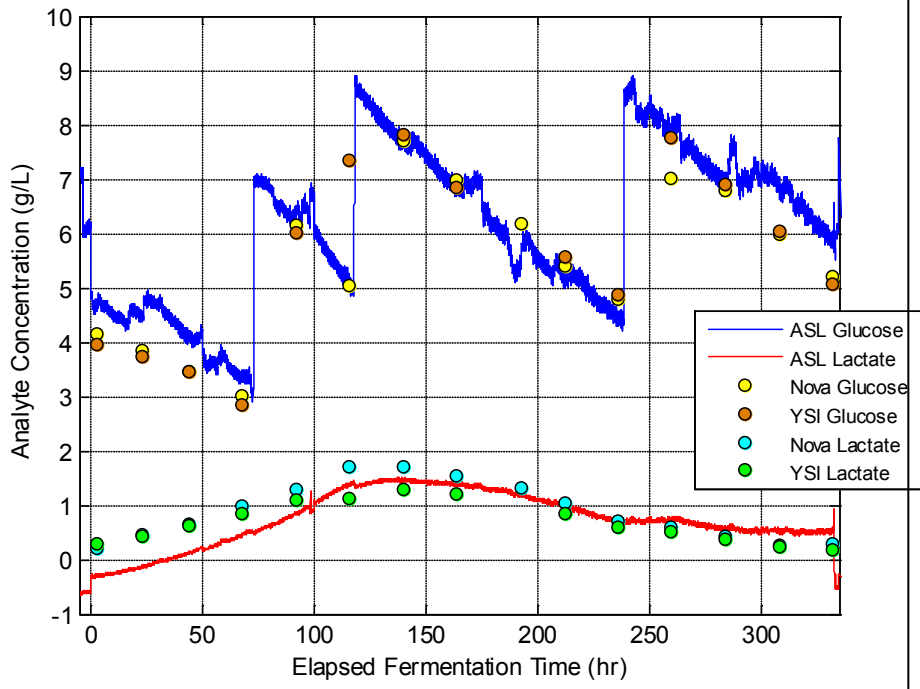
# Potential Next Gen SU Sensors:
## *Solid State NIR for Upstream Control*



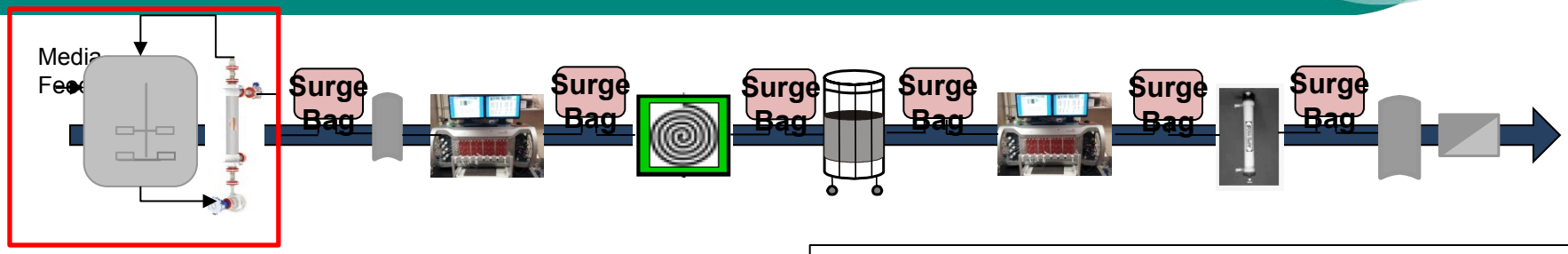

| *Pichia pastoris* | *CHO* | *E coli** |
|---|---|---|
| Glycerol, Methanol | Glucose, Lactate | Glucose, Acetate |
| Relative Cell Density | Relative Cell Density* | |



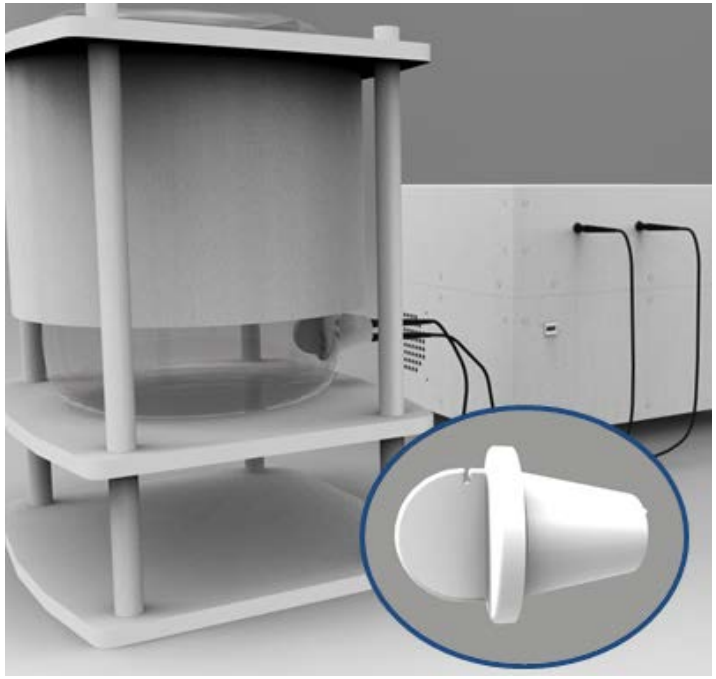

## Online NIR for glucose/lactate

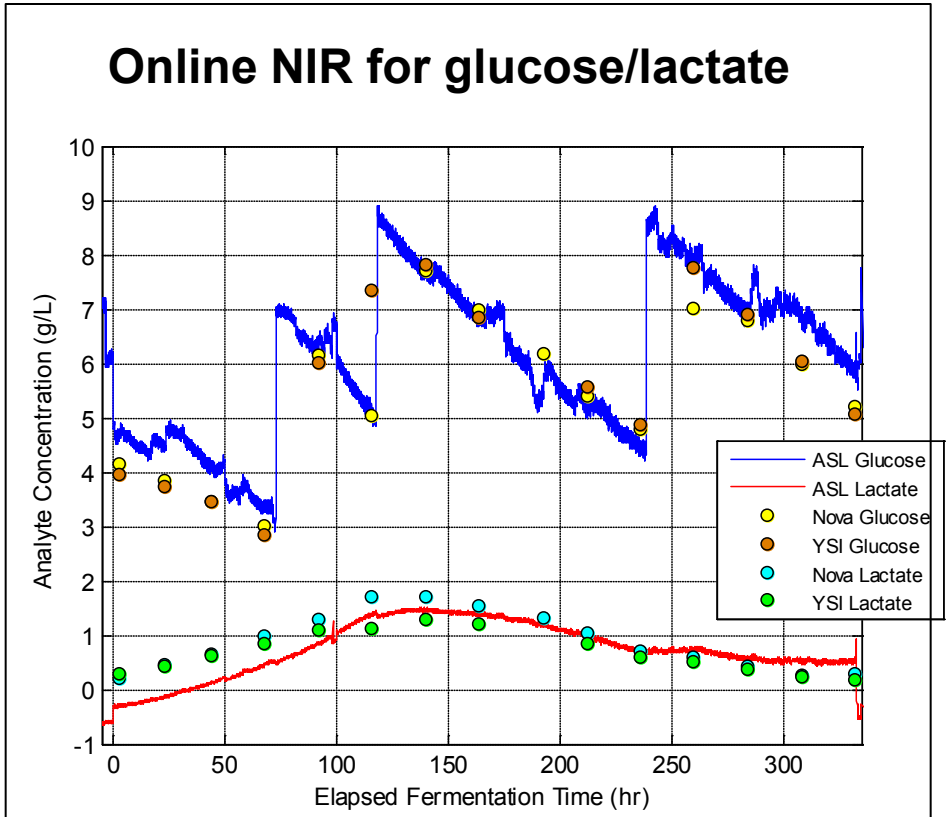


# Potential Next Gen SU Sensors:
## *Solid State NIR for Upstream Control*




Single Use Adapter in Development





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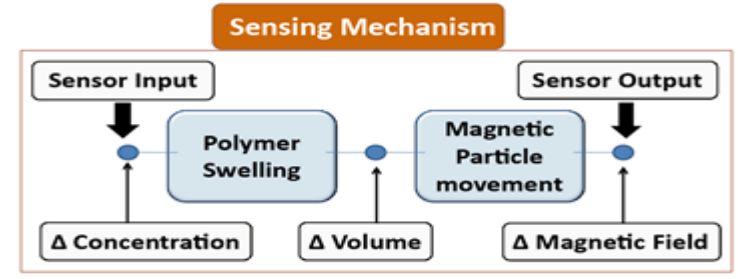
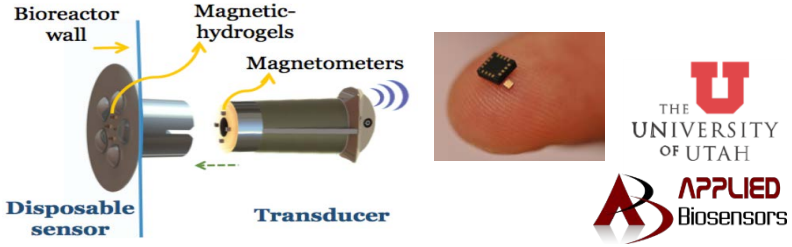
# Potential Examples for Future State

## *In situ* Sensing with Magnetic Smart Polymer

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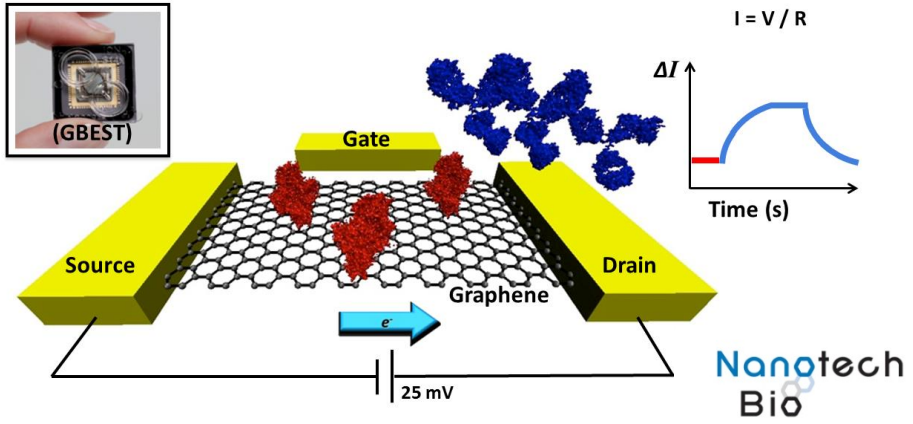
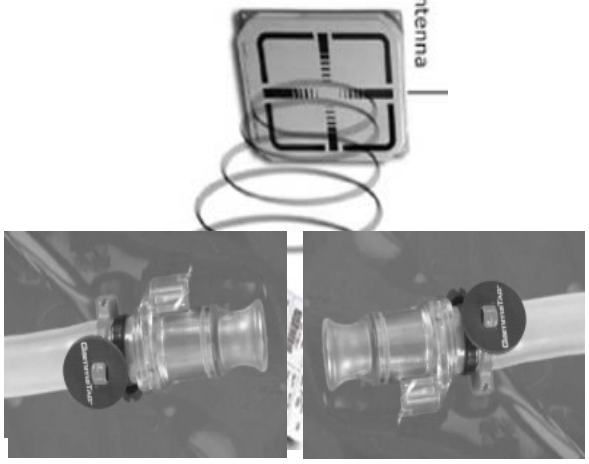
APPLIED Biosensors

## Graphene Bio-Electronic Sensing




Nanotech Bio

## *RFID SU Connection Verification*







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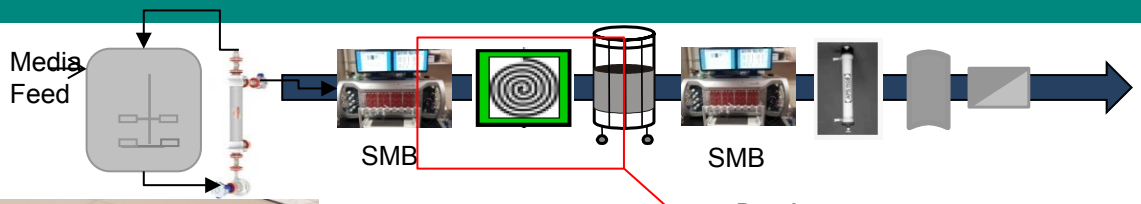
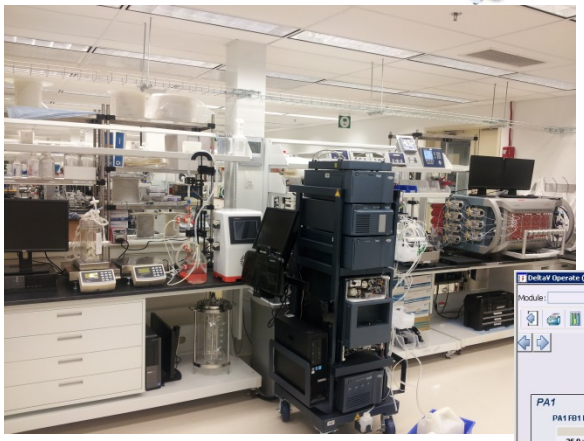
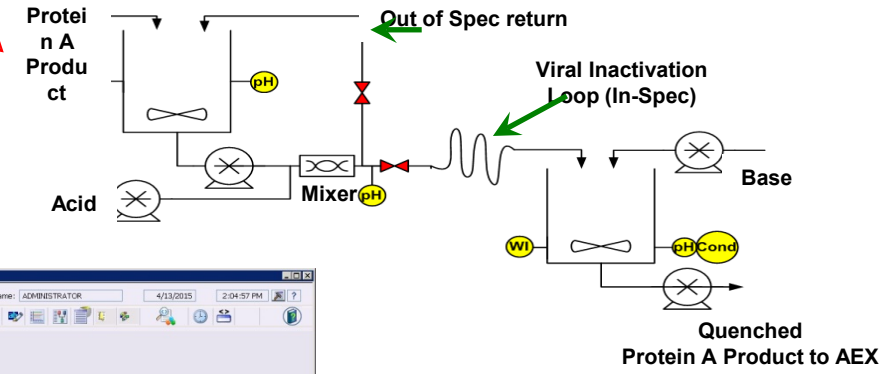
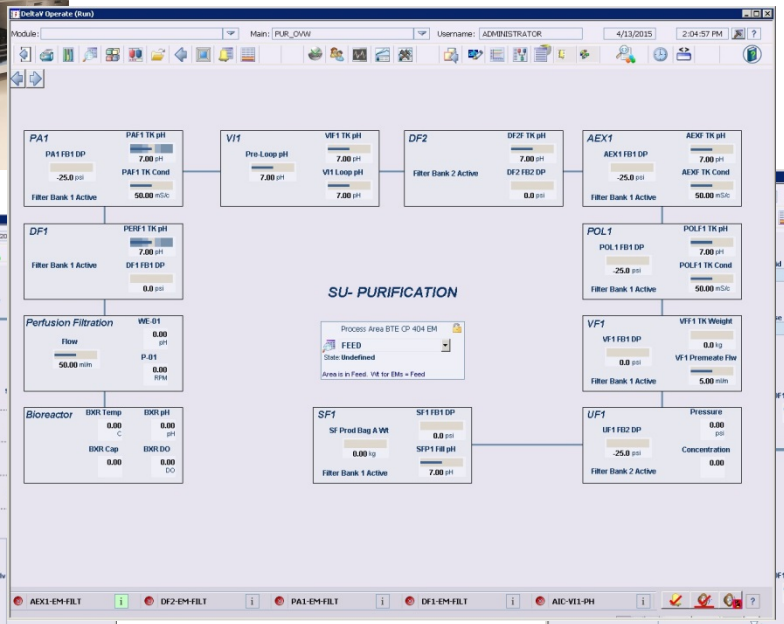
# Application Example : Continuous mAb Production

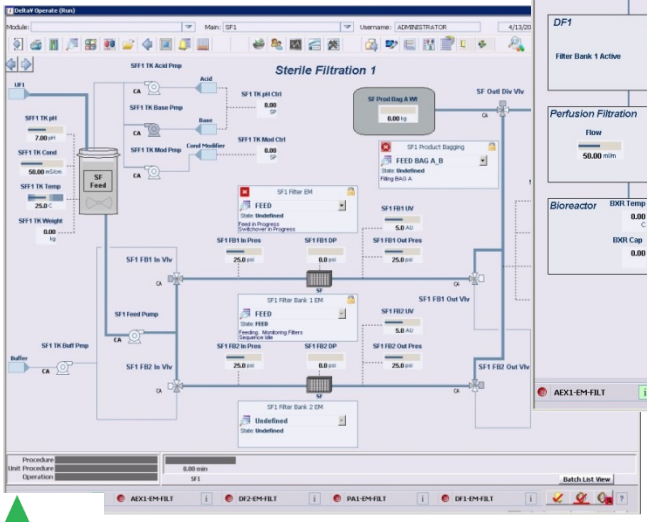
## *Protein Refinery Operations Lab (PRO Lab)*

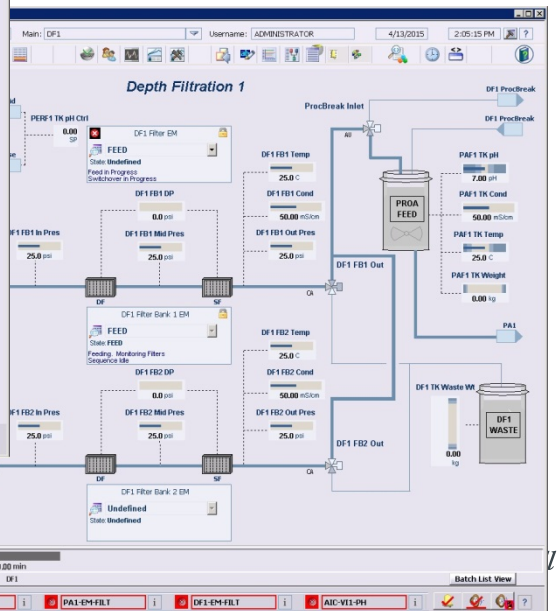




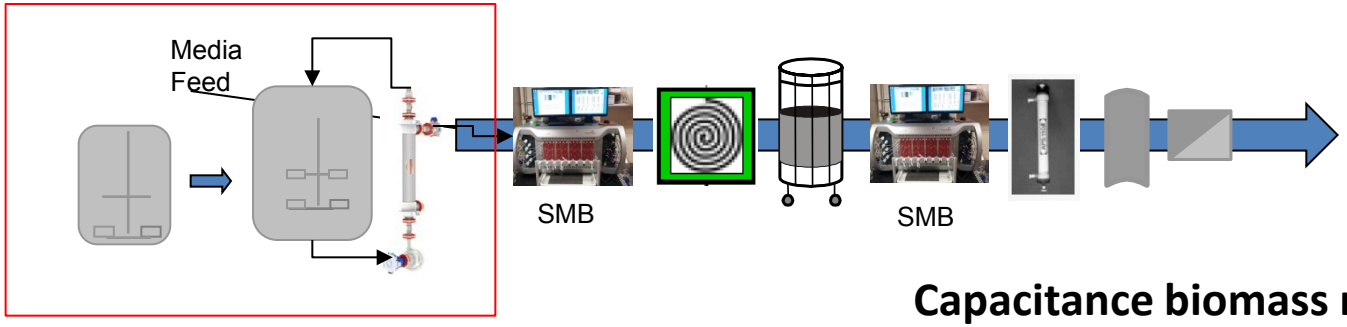



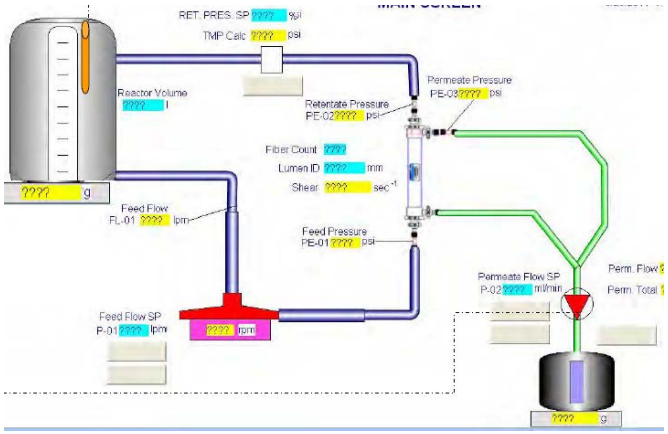



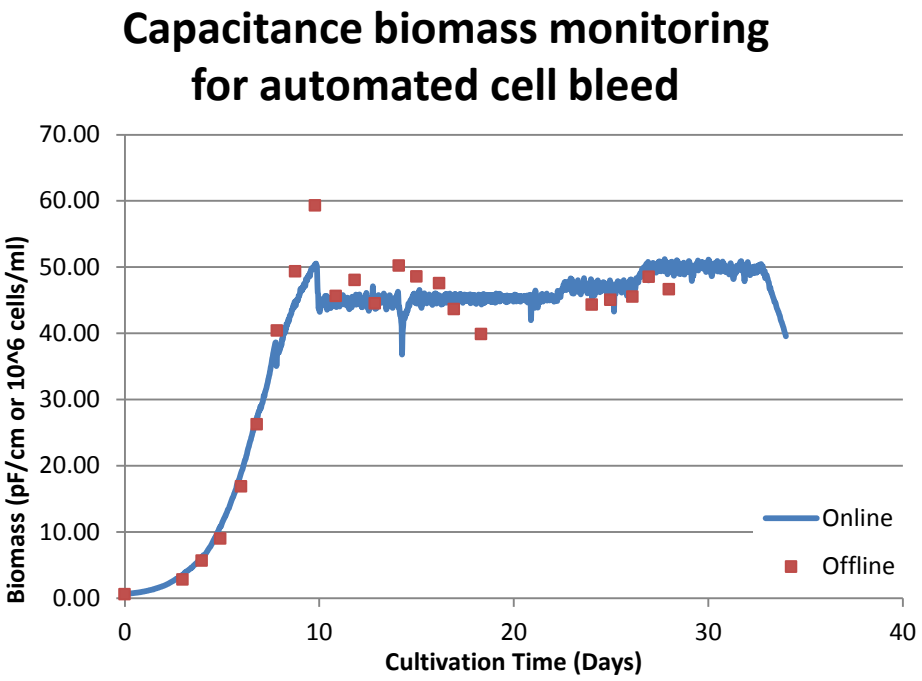




Public

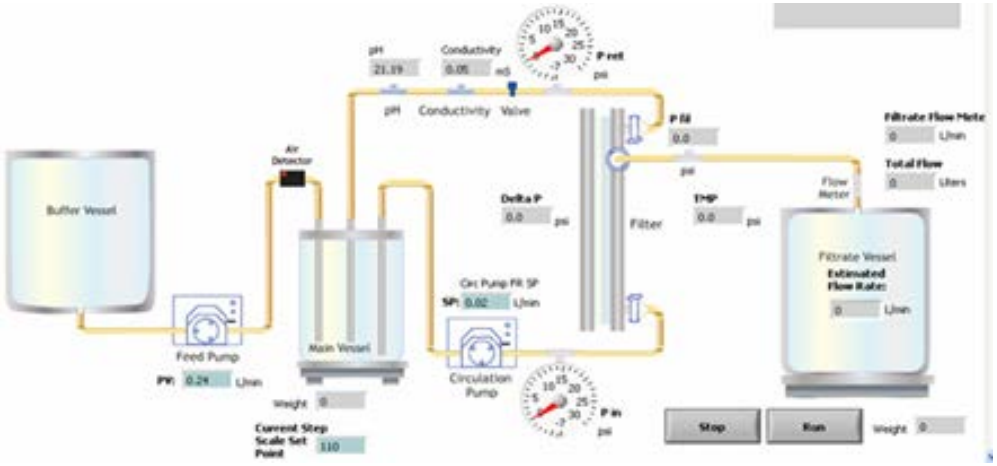
# Application Example:
## *Upstream perfusion*



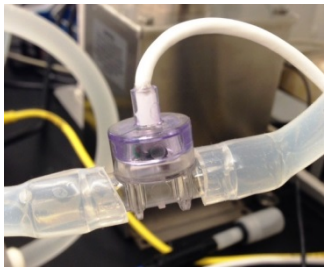



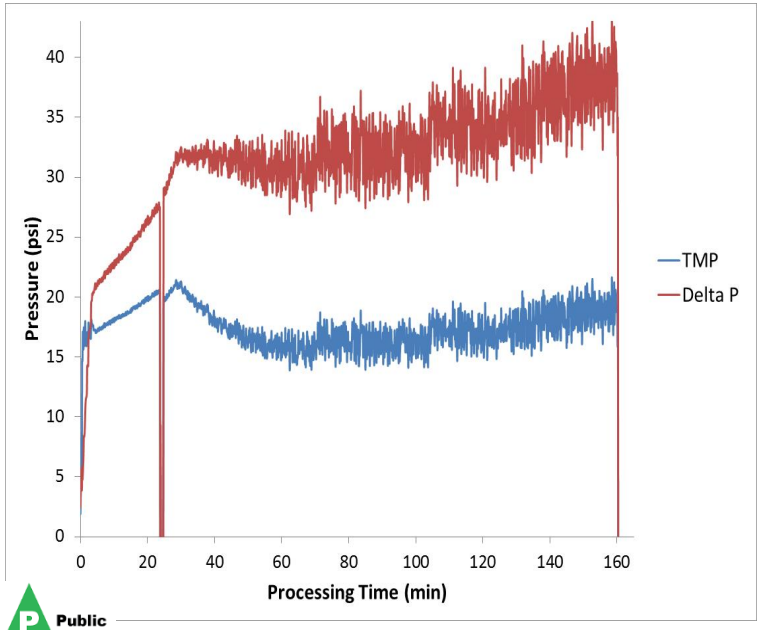
# Application Example:
## *Single Use Auto TFF for UF/DF*

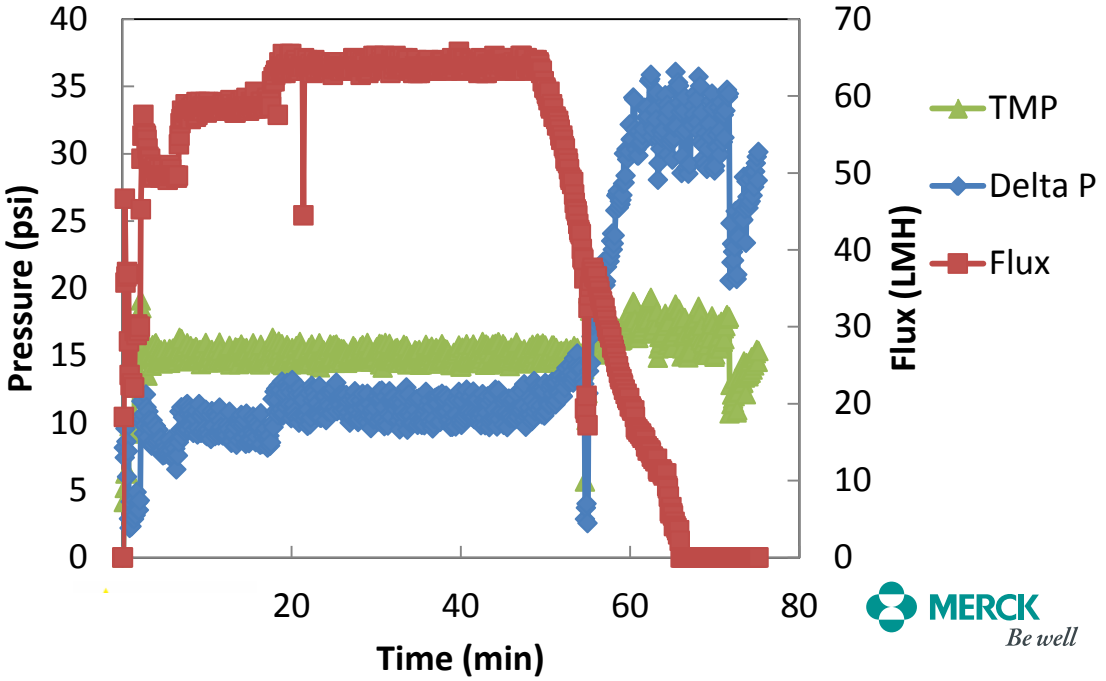



High concentration Development

- Real time SU pressure monitoring
- Enabling rapid process dev





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# SUMMARY

- **SU Sensors to be key part of Next Gen Bioprocessing**
  - The opportunity is NOW !!
- **Align on End user SU Sensor Expectations**
  - via BPOG User Group
- **Industry alignment of GMP Sensor Guidance**
  - Via BPOG / BPSA
- **Continue to openly Share & Collaborate on Technology gaps**

- ***Work together to improve reliability & robustness***

# Acknowledgements


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